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Indications and complications of androgen deprivation therapy

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Mostafid, Hugh ; Hermanns, Thomas

Abstract: **OBJECTIVE:** To review the indications for and side effects of androgen deprivation therapy (ADT) in men affected by prostate cancer. **DATA SOURCES:** National guidelines, evidence-based summaries, peer-reviewed studies, and websites. **CONCLUSION:** Indications for ADT include men with (1) intermediate- to high-risk localised prostate cancer undergoing radiation therapy, (2) biochemical recurrence after radical prostatectomy treated with salvage radiation therapy, or (3) metastatic prostate cancer. Several forms of ADT are available. To support self-management, body weight, diet, physical activity, alcohol consumption, and smoking should be discussed during clinical consultations. Important side effects of ADT may include flare-up phenomena of GnRH analogues, local reactions at injection sites, cardiovascular events, bone loss/fractures, drug-drug interactions, urinary tract dysfunction, hot flashes, cognitive impairment, seizure falls, and liver impairment. **IMPLICATIONS FOR NURSING PRACTICE:** Nurses have a role in personalized cancer care and should be familiar with indications, side effects, and interventions to optimize quality of life for men affected by prostate cancer receiving ADT.

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Indications and complications of androgen deprivation therapy

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ABSTRACT

Objective

To review the indication and side effects of androgen deprivation therapy (ADT) in men affected by prostate cancer.

Data Sources

National guidelines, evidence-based summaries, peer-reviewed studies, and websites.

Conclusion

Indications for ADT include men with (1) intermediate to high-risk localised prostate cancer undergoing radiation therapy, (2) biochemical recurrence after radical prostatectomy treated with salvage radiation therapy or (3) metastatic prostate cancer. Several forms of ADT are available. To support self-management body weight, diet, physical activity, alcohol consumption and smoking should be discussed during clinical consultations. Important side-effects of ADT may include flare-up phenomena of GnRH analogues, local reactions at

injection sites, cardiovascular events, bone-loss/fractures, drug-drug interactions, urinary tract dysfunction, hot flashes, cognitive impairment, seizure falls and liver impairment.

Implications for Nursing Practice

Nurses have a role in personalized cancer care and they should be familiar with indications, side effects and interventions to optimize quality of life for men affected by prostate cancer receiving ADT.

Keywords: Prostate cancer, Androgen deprivation therapy, Nursing, Side effects

INDICATIONS FOR ANDROGEN DEPRIVATION THERAPY

Prostate cancer (PCa) represents one of the most common neoplasms among men with almost 1'300'000 new cases and 360'000 deaths in 2018¹ accounting for 15% of all cancers diagnosed. Prostate cancer is the fifth leading cause of cancer death in men and represents 7% of total cancer mortality in men². The disease is driven by androgen steroid hormones, which activate the androgen receptor (AR) transcription factor³. Given this dependency on testosterone in order to grow, the function of the AR receptor represents the main therapeutic target approached by several different strategies and summarized by the umbrella term androgen deprivation therapy (ADT). Currently available forms of ADT include bilateral orchiectomy, Gonadotropin-releasing hormone (GnRH) analogues or antagonists and anti-androgens. The indications for ADT mainly include men with (1) intermediate to high-risk localised prostate cancer undergoing radiation therapy, (2) biochemical recurrence after radical prostatectomy treated with salvage radiation therapy or (3) metastatic prostate cancer.

Although there are many ways to target the AR, several clinical studies shed light which ADT should be initiated in which group of patients. Generally speaking there is no clear evidence in favor of orchiectomy, GnRH analogue or antagonist. However, in the specific case of patients

with impending spinal cord compression guidelines recommend either orchidectomy or GnRH antagonists over GnRH analogues because GnRH antagonists don't have the flare-up phenomena. In contrast, anti-androgens alone are only recommended in men with biochemical recurrence treated with salvage radiation therapy.

Because disease specific recommendations do not exist, logistic and economic considerations may help to choose a certain ADT. For patients without access to medical care on a regular base, orchiectomy may represent an ideal option. Whereas men refraining from a mutilating surgery with negative psychological consequences may be offered GnRH analogue or antagonist. As indicated in **Table 1**, GnRH analogue implants have the advantage of easier application and are the preferred option from a caregiver⁴ and economic⁵ perspective, particularly if administered at 6 monthly applications ⁶.

Despite ADT agents leading to response in nearly all metastatic prostate cancer patients, almost all patients will progress to castration resistant prostate cancer (CRPC), meaning that their cancer is growing despite castrate levels of testosterone. Advances in our understanding of the biology and progression mechanisms to CRPC has informed the development of next generation ADT drugs. Next generation ADT include abiraterone acetate (Zytiga®), enzalutamide (Xtandi®), apalutamide (Erleada®) and darolutamide (Nubeqa®) but can cost >50,000 \$ per patients per year and some specific caveats must be kept in mind. Given the high prevalence of men requiring ADT together with an increasing complexity of the disease, nurses can optimize supportive care for men receiving ADT ⁷ and have the responsibility of administration and monitoring response to therapy and side-effect, while being safely embedding in the multidisciplinary team⁷.

SIDE EFFECTS OF ANDROGEN DEPRIVATION THERAPY

Many men on ADT will grapple with side effects which can negatively affect physical and psychological outcomes, of both the man and his partner/spouse. Therefore, providing patient education and awareness to optimize supported self-management strategies may improve quality of life and the couples adjustment. Several side effects of ADT can at least partially be prevented or ameliorated by following a healthy diet⁸, maintaining a normal weight, engaging in physical activity^{9-11 12}, limiting alcohol consumption and smoking cessation. At each clinical consultation life-style modifications should be discussed, supported and encouraged by the healthcare professional to provide tailored self-management advice to meet the individual patients needs and preferences. In particular dietary instruction is also of importance regarding the timing of drug administration for example, abiraterone should be taken during fasting conditions. The following side effects are of clinical significance and are discussed in detail below.

Flare up

A unique consequence of GnRH analogues is the testosterone “flare-up” phenomenon which can be experienced for several days after the first injections and may lead to increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and cardiovascular death¹³. Therefore, to protect patients from experiencing the testosterone flare following the administration of GnRH, patients are also given a first-generation anti-androgen during the first 2-4 weeks after initiation of GnRH analogues¹³.

Local complications of ADT injections

As outlined in **Table 1** different GnRH analogues or antagonists are available. Although post-injection bruising has been reported more frequently with the implant compared with a reconstituted formulation, there were no observed differences in pain levels or the requirement

for analgesia in men receiving different administration of ADT agents ⁴. Nurses should take care and caution while injecting the implant into the anterior abdominal wall due to the proximity of underlying inferior epigastric vessels and its branches. In case of painful injections or hematoma nurses must monitor patients according to the local reaction observed. Patients with anticoagulation or cachexia should be given a reconstituted formulation instead of an implant. Moreover, the reconstituted formulation should be administered slowly and the needle should not be retracted too fast because this may lead to a local reaction if the skin comes into contact with the ADT formulation. Some of those local administration site reactions may be misinterpreted as an abscess in clinical practice which may result in unnecessary surgical removal for the patient.

Cardiovascular complications

After initiation of ADT men are likely to experience body weight gain, reduced insulin sensitivity and dyslipidemia¹⁴ therefore significantly increasing their risk for cardiovascular complications ¹⁵. We recommend a cardiology consultation for men with a history of cardiovascular disease, and for men older than 65 years prior to starting ADT ¹³. Furthermore, life-style modifications, close monitoring of blood pressure, lipid profile, and blood glucose levels is recommended ^{15,16}.

Bone loss and fractures

It has been observed that men receiving ADT show an increased bone turnover and decreased bone mineral density therefore increasing the risk of fractures. To reduce the risk of fractures life-style modifications, monitoring serum levels of vitamin D and calcium and early supplementation is recommended¹³. A personalized fracture risk assessment using the WHO FRAX tool (<http://www.shef.ac.uk/FRAX>) can be used in practice to decide whether a bone protective agent such as bisphosphonates or denosumab should be prescribed. Denosumab use is associated with an increased risk of osteonecrosis of the jaw and therefore, consultation with

a dentist before starting of denosumab is strongly recommended. After initiation of ADT regular screening for risk factors to prevent fractures is advised using dual energy radiographic absorptiometry (DEXA) ¹⁶.

Drug-drug interactions

Men affected by prostate cancer represents an aging population with high co-medication use for multiple comorbidities and increased risk of drug-drug interactions. Next-generation ADT agents differ regarding their drug-drug-interactions and these can be observed in up to 85% of men, which include medications such as opiates, proton-pump inhibitors, statins, alpha-blockers, anti-cholinergics and nifedipine ^{17,18}. Because such drug-drug interactions can have fatal complications we strongly advise to always assess co-medication and perform a new drug interaction test before choosing next-generation ADT agents.

Urinary tract function

Although ADT does decrease International Prostate Symptom Score (IPSS) patient self-reported scores, prostate volume ¹⁹ and increases urinary flow²⁰, men on ADT compared to healthy controls have a higher risk of experiencing lower urinary symptoms (LUTS) ^{21,22}. Around 15% of men may require urethral dilatation and/or transurethral resection of the prostate (TURP) within 5 years of receiving ADT ^{23 24}. To improve LUTS, alpha blockers ²⁵ as well as choosing GnRH antagonists instead of GnRH analogues have been suggested in a recent study ²⁶. Additionally, it should be kept in mind that the drug-drug-interaction of enzalutamide might minimize the efficacy of alpha-blockers and anti-cholinergics and therefore alternative options of next-generation ADT drugs should be considered. Progression of symptoms and the need for TURP is a worse predictor of cancer progression ²⁷ but TURP can safely be offered and successfully improves local symptoms in 80% ²⁸. Additionally, bilateral orchiectomy can be performed under the same anesthesia. Men on ADT have an increased risk of 20-30% ^{29 14} of developing acute kidney injury within the first year on ADT

which is 2.5 higher odds compared to the matched controls ³⁰. Urinary tract complications are frequent in men receiving ADT and therefore the benefit of regular assessment which should include urine flow, post void residual volume, renal sonography and creatinine assessment should be considered.

Loss of energy and strength

Loss of energy is often referred to as asthenia or fatigue and a common side effect in men undergoing ADT. Beside above-mentioned life-style modifications, screening for underlying diseases including anemia and hypothyroidism may offer therapeutic options to improve this debilitating side-effect in men. Similarly muscle loss is a common symptom ³¹ and therefore, referring patients to an exercise physiologist and dietitian can be helpful to improve energy levels, strength, physical conditioning, and mood in men receiving ADT.

Hot flushes

Hot flushes affect up to 75% of men treated with ADT but there are limited therapeutic options to alleviate this side-effect. There are several agents such as clonidine ³² and gabapentin ³³ which has demonstrated a limited efficacy in controlling hot flushes. Whereas, other agents which include estrogen ³⁴ or progestational ³⁵ have displayed a significant reduction in hot flushes but were associated with further side-effects. Despite limited evidence on the efficacy of such agents in controlling hot flushes, current clinical guidelines recommend prescribing a selective serotonin or noradrenergic reuptake inhibitors¹⁶. More recently, anti-cholinergics have been discussed as potential treatment options for hot flushes in prostate cancer patients ³⁶ as a clear efficacy has been shown in postmenopausal women ³⁷ and breast cancer survivors who were receiving tamoxifen or aromatase inhibitors ³⁸. However, further research is needed to test the mechanism effect of anti-cholinergic in men.

Sexual function and genital changes

A decrease in libido and erectile dysfunction is experienced in most patients on ADT, which can result in changes in the couple's relationship. A multidisciplinary ADT Survivorship Working Group suggested to prepare the couple for changes in sexual function and discuss couple centered goals and expectation before administering ADT. Sexual well-being interventions can be offered and discussed such as, phosphodiesterase 5 inhibitors, vacuum therapy to promote quality erections, transdermal estradiol for desire, and sexual therapy/mindfulness techniques³⁹. Noteworthy, the influence of estradiol on oncological and cardiovascular outcomes is unclear and should only be recommended with caution.

To ensure individualized couple preferences and needs are met, intervene early and discuss realistic expectation by promoting flexibility and talk in an open and nonjudgmental manner. Moreover, healthcare professionals should encourage intimacy despite low libido such as physical affection such as holding hands, hugging, physical touch, kissing, and cuddling to prevent erosion in spousal bond.

Increase in breast size or tenderness occurs in 90% of men with anti-androgens and 30% on GnRH analogue or antagonist and genital shrinkage including penile length and testicular size occurs in >90%⁴⁰. Either radiotherapy of the breasts⁴¹ or daily tamoxifen (20mg) could prevent gynecomastia^{41,42} and mastectomy or liposuction could be used to manage existing breast enlargement³⁹. Provide psychological support as men can experience feelings of embarrassment related to gynecomastia, review analgesia for pain/discomfort, and suggest the use of camouflage in clothing item selection.

Neuropsychiatric side-effects

Several retrospective studies suggested an association between ADT with cognitive impairment⁴³, Alzheimer's disease⁴⁴, depression⁴⁵, suicide and falls⁴⁶. As shown in localised prostate cancer patients group-based cognitive-behavioral stress management could improve quality of life^{47 48} whereas there are no definite recommendations to prevent or treat cognitive impairment. The additional negative impact of next-generation ADT needs to be clarified, specifically as they differ substantially regarding blood brain barrier penetration⁴⁹.

Liver function

Prostate cancer patients on ADT compared to men not on ADT may have an increased risk for liver diseases⁵⁰. Because hepatic impairment decreases the elimination of abiraterone, men treated with abiraterone are at risk for liver dysfunction and abiraterone is contraindicated in men with severe hepatic impairment^{18,51}.

Nursing Implications

Beside the many side-effects discussed above, it has to be expected that many other medical or social issues may arise during ADT for the man and his partner/spouse.

Each consultation with a patient and his partner/spouse is exceptionally unique and provides the healthcare professional with a very privileged glimpse into a person's life and concerns at that moment. A nurse consultation provides an opportunity to explore the patient's problems and identify areas of most concern to tailor intervention at the individual level of need which will invariably change over the cancer care continuum. Therefore, we would recommend regular screening by structured interviews, or patient reported outcome measures such as Holistic Needs Assessments (HNA) to identify areas of concern. Implementing paper and pen HNA in routine clinical practice means that men do not have to verbalise embarrassing concerns aloud, but instead the nurse can tactfully focus the consultation to the areas of most concern to the man and partner/spouse as identified in the HNA to ensure personalised and optimal care.

CONCLUSION

Nurses are a valuable contact for patients and their families and provide care co-ordination across the multidisciplinary team for men affected by prostate cancer receiving ADT. Nurses must be educated in the indications and side-effects of androgen deprivation therapy. Moreover, nurse should provide evidence-based interventions to alleviate side-effects, signpost patients for supportive care services in the community, and refer patients as appropriate to the MDT team. Given the complexity of prostate cancer therapies arising from ADT side effects nurses are the hub of cancer care to educate patients and families about expected side-effects of ADT, offered supported self-management to ultimately improve quality of life, costs and compliance of patients.

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Conflicts of interest

There are no conflicts of interests.

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Drug	Goserelin acetate	Leuprorelin acetate	Leuprorelin acetate	Leuprorelin acetate	Triptorelin acetate	Buserelin acetate	Degarelix acetate	Abarelix
Brand name¹	Zoladex [®]	Leuprorelin Sandoz [®]	Lupron Depot [®]	Eligard [®]	Decapeptyl [®] SR	Suprefact [®]	Firmagon [®]	Plenaxis [®]
Mode of action	LHRH-Agonist	LHRH-Agonist	LHRH-Agonist	LHRH-Agonist	LHRH-Agonist	LHRH-Agonist	LHRH- <u>Antagonist</u>	LHRH- <u>Antagonist</u>
Preparation	Implant	Implant	Microspheres	Powder ²	Powder ^{2,3}	Implant	Powder ²	Powder ²
Administration	s.c.: any time	s.c.: any time	s.c./i.m.: immediately	s.c.: immediately	s.c./i.m.: immediately	s.c.: any time	s.c.; within 60 min	i.m.
Flare protection needed	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Dose	Always same dose	Always same dose	Always same dose	Always same dose	Always same dose	Always same dose	First dose 2x120mg Regular dose 80mg	Always same dose
Dosing frequency	1-, or 3-monthly	1-, or 3-monthly	1-, 3-, 4- or 6-monthly	1-, 3-, 4- or 6-monthly	1-, 3-, or 6-monthly	2-, 3-, monthly	1-monthly	2-weekly
Storage conditions	<25°C	<30°C	<30°C	2-8°C	<25°C	<25°C	<25°C	<25°C

<i>Needle diameter</i>	14-16G	14G	21-23G	18-20G	19-21G		25G	18G
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Table 1 Overview of advantages and disadvantages of available LHRH Agonists and Antagonists,

¹varies by country, ² needs Up to 15 minutes to dissolve, ³ needs time to reach room temperature

Abbreviations LHRH: luteinizing hormone-releasing hormone, s.c.: subcutaneous, i.m.: intramuscular, °C: Degree Celsius, G: gauge